Effect of trait anxiety on prefrontal control mechanisms during emotional conflict

Magali Comte, Aïda Cancel, Jennifer T Coull, Daniele Schön, Emmanuelle Reynaud, Sarah Boukezzi, Pierre-François Rousseau, Gabriel Robert, Stéphanie Khalfa, Eric Guedj, et al.

Effect of trait anxiety on prefrontal control mechanisms during emotional conflict

Magali Comte[1], Aïda Cancel[1], Jennifer T Coull[2], Daniele Schön[3], Emmanuelle Reynaud[1], Sarah Boukezzi[1], Pierre-François Rousseau[1], Gabriel Robert[4], Stéphanie Khalfa[1], Eric Guedj[1], Olivier Blin[1,5], Daniel R. Weinberger[6], Eric Fakra[1,5,7]*

[1]Institut de Neurosciences de la Timone, UMR 7289, Aix-Marseille Université & CNRS, Marseille, France.

[2]Laboratoire des Neurosciences Cognitives, UMR 7291, Pôle 3C, Aix-Marseille Université & CNRS, Marseille, France.

[3]INS, UMR 1106, Aix-Marseille Université & INSERM, Marseille, France

[4]EA 4712 Comportement et Noyaux Gris Centraux, Faculté de médecine Université Rennes 1, Rennes, France.

[5]CIC-UPCET et Pharmacologie Clinique, Hôpital de la Timone, Marseille, France

[6]Lieber Institute for Brain Development, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

[7]Service Hospitalo-Universitaire de Psychiatrie Secteur Saint-Etienne, Hôpital Nord, Saint-Etienne, France.

* Corresponding author: Eric Fakra, M.D., Ph.D.

CHU Saint-Etienne

Service Hospitalo-Universitaire de Psychiatrie

Hôpital Nord, 42055 Saint-Etienne cedex 2

Tel: + 33 (0)4 77 12 74 06

Fax: + 33 (0)4 77 82 88 57

Email : eric.fakra@chu-st-etienne.fr

Abbreviated title: Anxiety and emotional conflict

Key words: anterior cingulate cortex, lateral prefrontal cortex, emotional conflict, fMRI, psychophysiological interaction, trait anxiety

Abstract: Converging evidence points to a link between anxiety proneness and altered emotional functioning, including threat-related biases in selective attention and higher susceptibility to emotionally ambiguous stimuli. However, during these complex emotional situations, it remains unclear how trait anxiety affects the engagement of the prefrontal emotional control system and particularly the anterior cingulate cortex (ACC), a core region at the intersection of the limbic and prefrontal systems. Using an emotional conflict task and functional magnetic resonance imaging (fMRI), we investigated in healthy subjects the relations between trait anxiety and both regional activity and functional connectivity (psychophysiological interaction [PPI]) of the ACC. Higher levels of anxiety were associated with stronger task-related activation in ACC but with reduced functional connectivity between ACC and lateral prefrontal cortex (LPFC). These results support the hypothesis that when one is faced with emotionally incompatible information, anxiety leads to inefficient high-order control, characterized by insufficient ACC-LPFC functional coupling and increases, possibly compensatory, in activation of ACC. Our findings provide a deeper understanding of the pathophysiology of the neural circuitry underlying anxiety and may offer potential treatment markers for anxiety disorders.

Introduction

Vulnerability to anxiety is associated with negative emotional biases in selective attention [Mathews et al., 1997; Bar-Haim et al., 2007] and higher susceptibility to emotionally ambiguous stimuli [Hirsch and Mathews, 1997; Richards et al., 2002]. These impairments in emotional processing appear to be linked to an imbalance in amygdala-prefrontal circuitry, which promotes threat-related responses [Bishop, 2007], and to contribute to the development and maintenance of anxious symptoms [Mathews and MacLeod, 2002]. A predominant hypothesis is that anxiety potentiates a pre-attentive threat-evaluation system [Rauch et al., 2000]. Accordingly, increased amygdala BOLD signal has been observed in anxious volunteers in response to threat-related distractors [Bishop et al., 2004b, 2006]. Nonetheless, more recent evidence associates anxiety with altered prefrontal engagement, including the lateral prefrontal cortex (LPFC) and anterior cingulate cortex (ACC), during attentional and interpretative processes [Bishop, 2007; Krug and Carter, 2010; Campbell-Sills et al., 2011].

ACC has a strategic position at the crossroads of the cortico-limbic circuit and extensive reciprocal connections with both the lateral prefrontal cortex [Saleem et al., 2014] and subcortical limbic regions, such as the amygdala [Van Hoesen et al., 1993], making it ideally suited for emotion-cognition integration. Accordingly, ACC is implicated in a complex set of functions, including modulation of attention, response selection/inhibition, and monitoring of competition, as well as appraisal of emotional information and regulation of affective responses [Bush et al., 2000]. In addition, ACC has been implicated in selective attention to emotional information, particularly in the detection of conflicting response

tendencies [Bush et al., 2000; Etkin et al., 2006]. Altered functioning of ACC features prominently in the pathophysiology of anxiety disorder [Shin and Liberzon, 2010].

A more detailed analysis of brain function associated with anxiety involves analysis of dynamic cortical processing across brain regions rather than in specific brain areas [Seeley et al., 2007; Etkin et al., 2010]. Neuroimaging studies have started to investigate the impact of anxiety proneness on functional coupling during basic emotional tasks. These studies have mainly reported reduced functional coupling between amygdala and ACC/medial prefrontal (mPFC) regions [Kienast et al., 2008; Sripada et al., 2013; Gee et al., 2013], possibly reflecting the failure of mPFC to suppress amygdala activity [Pezawas et al., 2005]. In parallel, anxiety has been shown to predict defective functional interactions between prefrontal regions in cognitive tasks and at rest [Seeley et al., 2007; Basten et al., 2012] notably between LPFC and dorsal ACC in conflict conditions [Basten et al., 2011].

However, the effects of trait anxiety on the integrated prefrontal emotional control system during more complex emotional situations, such as conflicting emotional stimuli, are poorly known. This is unfortunate because conflicting emotional signals are abundantly present in everyday life and are crucially involved in social interactions. We propose to explore the relations between healthy participants' trait anxiety and variation in ACC activity and in functional connectivity during an emotional conflict task. The study focuses primarily on ACC, given its central role in processing conflicting information, and on its functional interactions with LPFC and amygdala, two regions strongly engaged in emotionally incongruent conditions [Etkin et al., 2006; Comte et al., 2014] and whose activity is modulated by anxiety severity [Bishop et al., 2004a, 2006; Ewbank et al., 2009].

Based on the link between anxiety and perturbed prefrontal functioning found in previous studies, we expected that trait anxiety magnitude would be associated with altered

ACC BOLD response [Bishop et al., 2004a; Bishop, 2007] and decreased functional coupling between ACC and LPFC during emotional conflict [Basten et al., 2011].

Materials and Methods

Participants

The present study was conducted with 25 participants (9 women; 20-47 years old, mean age= 33 ±7.5 years old). All participants were right-handed according to the Edinburgh Handedness Inventory [Oldfield, 1971]. The non-patient version of the Structured Clinical Interview for DSM-IV (SCID; [First et al. 2002]) was used to ensure the absence of psychiatric disorder or psychiatric history. Participants had no current or past serious medical or neurological condition; they were not taking any psychotropic drugs at the time of the study and had no contraindication for MRI.

This study was conducted in accordance with the principles of the declaration of Helsinki. Approval was obtained from the local ethics committee (Comité de protection des personnes, Marseille). Each participant gave informed written consent before entering the study.

Stimuli and procedure

In the experimental task (Variable Attention and congruency Task [VAAT] [Comte et al., 2014]), participants were presented images composed of two parts. The central part of the image displayed photographs of faces expressing positive emotion (joy) or negative emotion (fear, disgust, or anger), from the NimStim Face stimulus set [Tottenham et al., 2009]. The peripheral part, on which the face images were superimposed, represented scenes with a pleasant or unpleasant emotional content, extracted from IAPS files [Lang et al., 2008].

Subjects had to focus on the part of the image framed in green (either the face or the scene) and determine its emotional content (pleasant versus unpleasant) by pressing the corresponding key.

The task consisted of 3 X 2 conditions varying according to emotional congruency (same or different emotional content in the face and the scene), emotional valence (positive or negative), and attentional load (attention focused on the face (low attention) or on the scene (high attention)). Because our primary interest in this study was the effect of trait anxiety on ACC functional activity and connectivity during emotional conflict, we focused the analyses on BOLD signal changes induced by the emotional congruency parameter variation (incongruent versus congruent trials). Relative to congruent conditions, incongruent ones elicited increased activation of the ACC as well as a significantly higher functional connectivity (PPI) between ACC and LPFC, as well as between ACC and amygdala [Comte et al., in press].

The task had a mixed event-related/block design, comprising four sessions of 6 min 8 sec each. The sessions were divided into 16 blocks that each lasted 20.4 sec. Each block comprised 4 experimental trials, each lasting 3000 ms, during which subjects provided their response. The valence parameter varied from trial to trial whereas the congruency and attention parameters varied from block to block. The inter-stimulus interval (ISI) and inter-block interval (IBI) were randomly jittered with a respective mean of 1.4 and 1.6 sec. Block order was randomized within sessions, and the order of the sessions was counterbalanced across subjects.

MRI acquisition

Data were acquired on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker). After an initial localizing scan, functional data were acquired using a T2*-weighted gradient echoplanar imaging (EPI) sequence (TR= 3000 ms; TE=30 ms; FOV= 19.2 × 19.2; 64 × 64 matrix; flip angle 84.8; voxel size 3x3x3 mm^3). Four functional runs of 45 interleaved axial slices were acquired along the anterior-posterior commissure plane with a continuous slice thickness of 3 mm. After the fMRI scans, high-resolution anatomical images were acquired for anatomical identification with a sagittal T1-weighted MP-RAGE sequence (TR= 9.4ms; TE=4.42ms; TI= 800ms; 256 × 256 × 180 matrix; flip angle 30; voxel size 1x1x1 mm^3).

Self-report anxiety measures

Before fMRI sessions, participants completed the Spielberger State-Trait Anxiety Inventory (STAI, [Spielberger, 1983]). Participants' state anxiety scores ranged from 24 to 58 (mean=33.5, SD=8), and trait anxiety scores from 23 to 57 (mean=37.2, SD=8). These scores are similar to the published norms (state: mean = 36, S.D. = 10; trait: mean =36, S.D. =10 [Spielberger, 1983]. To test the potential association between trait and state anxiety, a Pearson correlation analysis was performed between these two variables. In case of significant correlation, or a trend to a significant correlation ($p< 0.1$), another set of analyses were performed adding STAI state scores as covariate in order to disentangle the effects of trait anxiety form those of state anxiety.

Behavioral data analysis

Behavioral data consisted of reaction time and accuracy rate. To investigate the effect of trait anxiety on task performance, linear regression analyses were performed with, separately, response times (RTs) and accuracy as dependent variables, gender, and age as covariates. The threshold for statistical significance was P <0.05. Behavioral data were analyzed in SPSS (v18.0).

fMRI data analysis

All data were analyzed using SPM8 software (Wellcome department of Cognitive Neurobiology, University College London; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The first four volumes of each session, corresponding to signal stabilization, were excluded from the analysis. We performed standard preprocessing procedures, including slice timing correction, motion correction, EPI co-registration to the T1 image, normalization into the MNI (Montreal Neurological Institute) space, and smoothing with a 6 mm Gaussian kernel.

The pre-processed functional images were analyzed using a General Linear Model and an event-related approach. Congruent and incongruent trials were separately modeled and convolved with a canonical hemodynamic response function to form regressors. The six movement parameters were included in the analysis as regressors of no interest to model residual effects due to head motion. A 128 s high-pass filter was applied to the data to remove low-frequency noise. For each participant, contrast images were calculated to estimate BOLD signal changes due to variation in emotional congruency (incongruent versus congruent conditions). The individual contrast images were then entered into a second-level random effect model. We performed multiple regression analyses as implemented in SPM8, in which subjects' trait anxiety scores, age, and gender were entered as covariates. T-contrasts were applied to identify brain regions whose activity in response to the emotional

congruency variation was positively or negatively associated with STAI anxiety scores. We used a region of interest approach (ROI) focusing on the ACC. ACC ROI was functionally defined using an 18 mm (diameter) sphere centered on peak activations derived from an earlier study examining emotional conflict [Etkin et al., 2010]. The MNI coordinates for the center of this spherical ROI were the following: ACC (x=5, y=33, z=31). We report results within this ROI, using small-volume corrections ($p<0.05$, family-wise error (FWE) corrected at the voxel level).

Functional Connectivity Analyses:

Psychophysiological interaction (PPI) analyses [Friston et al., 1997] were used to assess to what extent the ACC functional connectivity to LPFC and amygdala was modulated by the emotional congruency parameter (incongruent versus congruent conditions). For each subject, the seed region was determined, using a subject-specific local maximum that was within 15 mm of the group maximum and within the ACC anatomical mask. The first eigenvariate time series of the BOLD-signal, adjusted for the effects of interest, was extracted from a 5 mm sphere around the seed coordinates. A time series was calculated with the first eigenvariate from the time series of all voxels within the sphere. The PPI regressor was calculated as the product of the time series of the seed region (physiological factor) and the vector coding for the congruency parameter (psychological factor). The general linear model for the first level PPI analyses included the physiological, psychological, and interaction terms, as well as the nuisance variables described above. The individual contrast images testing for a PPI between the ACC and voxels in the other two regions of interest were then entered into second-level random effect analyses, in exactly the same way as the second level analyses above. To test the effect of trait anxiety on the seed region

connectivity, we employed a regression model within SPM, in which STAI scores, age, and gender were entered as covariates. These analyses served to identify brain regions showing congruency-related changes in connectivity with ACC, positively or negatively associated with anxiety scores. Our analyses focused on two regions of interest (ROIs): the LPFC and amygdala. ROIs were created bilaterally using an 18 mm (diameter) sphere for the LPFC and a 12 mm (diameter) sphere for the amygdala. ROIs centers correspond to peak activations reported in earlier studies exploring emotional conflict and reporting strong LPFC activation [Ochsner et al., 2009], and ACC-amygdala connectivity [Etkin et al., 2010] in conflict condition. The MNI coordinates for the center of these ROIs were as follows: LPFC (x=±58, y=22, z=20); amygdala (x=±22, y=-2, z=-18). We report results within our ROIs, using small-volume corrections ($p<0.05$, FWE at the voxel level). Anatomical localization of brain functional activity and connectivity was assessed using WFU PickAtlas software [Maldjian et al., 2003].

Results

Self-report anxiety measures

The Pearson correlation analysis revealed a trend for trait anxiety to be positively associated with state anxiety ($r=0.375$; $P=0.065$).

Behavioral data

Participants' accuracy was high, with a mean value of 92.8 % (SD= 9.8). Overall mean reaction time was 1345 ms (SD= 254). Regression analyses revealed a trend for STAI-trait scores to be positively associated with longer reaction time (β= 0.455; p=0.051) and higher error rate (β= 0.256; p=0.090) in incongruent versus congruent conditions.

Imaging Data

Relations between brain activity and trait anxiety scores:

Regression results indicated that trait anxiety was positively associated with the recruitment of ACC (*x, y, z*= 4, 26, 28; k=24; T= 4.34; *P (*FWE) =0.024) in incongruent relative to congruent conditions (Fig. 1). This cluster corresponded to Brodmann area 24 and 32. Similar results were obtained when controlling for state anxiety (ACC: x, y, z= 4, 26, 28; k=15; T= 4.02; P (FWE) =0.046). This finding is in line with trait anxiety being linked to increased engagement of ACC when emotional conflict occurs.

Relations between functional connectivity and trait anxiety score:

The PPI analysis revealed a negative relation between trait anxiety and the functional connectivity between the ACC seed region and the right LPFC (*x, y, z*= 54, 24, 18; k= 31; T= 4.14 *P (*FWE) =0.041) in incongruent compared to congruent conditions (Fig. 2). This cluster corresponded to Brodmann area 45. Similar results were obtained when controlling for state anxiety (right LPFC: x, y, z= 54, 24, 18; k= 18; T=3.90 P (FWE) =0.066), albeit the relation no longer survived FWE voxel-wise correction. This indicates that the higher the trait anxiety scores, the weaker the coupling between ACC and LPFC in situations of emotional conflict. In

contrast, there was no significant modulatory effect of trait anxiety on ACC-amygdala functional coupling.

Discussion

The present study investigated the impact of anxiety proneness on ACC activity and functional connectivity while subjects performed an emotional conflict task. Findings revealed that in response to emotional conflict, subjects' trait anxiety was positively associated with the magnitude of ACC activity but negatively coupled with the strength of functional connectivity between ACC and right LPFC.

The association found between the ACC activity and individual STAI-trait scores converges with previous neuroimaging studies reporting an impact of anxiety on prefrontal control systems and more specifically ACC recruitment in both cognitive and emotional tasks [Bishop et al., 2004a; Bishop et al., 2006; Campbell-Sills et al., 2011; Forster et al., 2013]. As stated before, through its privileged interactions with both executive lateral prefrontal regions and limbic emotional structures, ACC exercises a range of top-down control functions over emotional processing [Bush et al., 2000; Phillips et al., 2008] such as affective conflict monitoring [Etkin et al., 2006; Ochsner et al., 2009].

Anxiety disorders and high trait anxiety are accompanied by a bias in selective attention towards negative/threat-related stimuli [Mathews et al., 1997; Bar-Haim et al., 2007]. Although most neuroimaging research on selective attention in anxiety has focused on the amygdala, some studies have linked this behavioral deficit to altered activity within prefrontal control regions, notably in ACC, in volunteers with high versus low levels of

anxiety [Shin et al., 2001; Bishop et al., 2004a, 2006], suggesting that heightened anxiety leads to impaired recruitment of ACC top-down control on emotional processing. In addition, anxious individuals show negative interpretative biases when attempting to disambiguate affective information [Richards et al., 2002]. Ambiguity processing happens when decision-making relies on information that does not clearly suggest the selection of one option over another, because the information is incomplete, contradictory, or unclear [Simmons et al., 2008]. It is known that appraisal of emotional ambiguity involves a network of brain regions comprising ACC [Simmons et al., 2006]. Interestingly, one other study has shown altered ACC activity in anxiety-prone subjects processing ambiguous sets of emotional facial expressions [Simmons et al., 2008]. Thus, our findings echo and extend these lines of investigation by indicating perturbed engagement of ACC linked to trait anxiety, possibly to overcome ambiguity arising from discordant affective information.

Results are, however, inconsistent regarding whether anxiety is associated with reduced or increased ACC engagement. Some studies have shown stronger "compensatory" activation [Paulus et al., 2004; Campbell-Sills et al., 2011] whereas other evidence points to decreased "insufficient" activation in high relative to low anxious participants, along with equal or lower levels of performance [Bishop et al., 2004a, 2006]. Potential explanations for this discrepancy may come from variations in task demands, motivational factors, task performance, or the opportunity to prepare for task performance [Eysenck and Derakshan, 2011]. Our results appear consistent with attentional control theory [Eysenck and Derakshan, 2011], which predicts that high anxious individuals should show stronger brain activation, reflecting compensatory increases in neural effort and processing resources expended on task performance, in the effort to maintain good performance. However, a

more parsimonious interpretation is that conflicting, emotionally charged stimuli induce a lesser "tuned activity" profile in anxious individuals [Winterer et al., 2006].

As we expected, connectivity analysis revealed a negative relation between trait anxiety and connectivity strength between ACC and right LPFC in incongruent relative to congruent conditions. It is assumed that to resolve conflict on incongruent trials, there has to be an effective interaction between ACC and LPFC where inputs from ACC signal the occurrence of conflict and lead to the recruitment of control mechanisms implemented by LPFC [Kerns et al., 2004; Egner and Hirsch, 2005]. A negative association between trait anxiety and functional connectivity between ACC and LPFC in conflict trials has been highlighted in a previous study using a color word Stroop task [Basten et al., 2011]. Our finding suggests that the diminished interplay between these prefrontal regions extends to situations in which both the task-related and distractor stimuli are emotional. Insofar as the attenuated functional coupling of ACC and LPFC associated with trait anxiety is accompanied by a significantly stronger activation of ACC during incongruent trials, it is tempting to speculate that the exaggerated activation of ACC reflects a local compensation for deficient connectivity between this structure and LPFC. But here again, increased activation could, rather, reveal greater "noise" within ACC, and consequently, reduced likelihood that this region is as efficiently in phase with LPFC. Furthermore, the link seen here between vulnerability to anxiety and impoverished functional coupling between prefrontal regions supports the emerging view that psychiatric disorders arise as a result of abnormal integration or "dysconnection" between brain regions [Weinberger et al., 1992].

We did not find a significant relation between trait anxiety and functional coupling between ACC and the amygdala. The association between amygdala engagement and individual variation in trait anxiety has not consistently been found [Bishop et al., 2004a;

Campbell-Sills et al., 2011; Goldstein et al., 2013] . Previous works have shown weakened top-down control of ACC/mPFC over amygdala in anxious individuals [Kienast et al., 2008], but impairment in ACC-amygdala coupling has been noticed mainly in very simple emotional tasks or at rest [Pezawas et al., 2005 ; Kim et al., 2011]. One explanation may be that the emotional conflict task employed here, which mainly mobilized the prefrontal control processes rather than the emotional appraisal processes, could not uncover the effect of anxiety on limbic connectivity. Yet, Etkin et al. [2010] found dampened connectivity between ACC and the amygdala during the resolution of emotional conflict. That study, however, was conducted on clinical patients diagnosed with generalized anxiety disorder and not on healthy volunteers as in our study. We can thus speculate that the failure of ACC to inhibit the amygdala might be related to the symptomatic outcome of a clinical condition, rather than simply vulnerability to anxiety.

This study has some limitations. First, it could be argued that given the positive trend observed between trait and state anxiety scores, it is difficult to attribute the modulatory effects on prefrontal control mechanisms to trait anxiety scores only. To control for possible effects of state anxiety, we repeated the analyses adding state anxiety scores as nuisance covariate. The pattern of results was similar to that previously obtained, though less marked. This could be explained by a decrease in statistical power due to the addition of a third covariate, especially in the case of PPI analyses, which generally tend to lack power and generate a high proportion of false negatives [O'Reilly et al., 2012]. This suggests that even though an effect of state anxiety on our findings cannot be entirely ruled out, this effect is minor compared with that of trait anxiety. Second, the current study relies on self-report measures of anxiety. Studies have consistently shown individual differences in the manner of response to self-report items in such a way that the trait that is measured might be affected

by other aspects of the subject's personality [Austin et al., 1998]. Thus, self-measures may be influenced by a number of factors including participants' honesty, introspective ability, understanding/interpretation of the questions, and response styles (Ex: extreme responding, i.e. tendency to opt for the extremes of the response scale). Finally, although cannabis consumption constituted an exclusion criterion and none of the subjects reported using cannabis at the time of the study, we did not test for recent use of cannabis, and therefore the interference of such a confounding factor cannot be entirely ruled out.

Conclusion

Our findings, in line with previous works [Shin et al., 2001; Bishop et al., 2004a, 2006; Basten et al., 2011, 2012], suggest that dysfunction of prefrontal control mechanisms constitutes a core process in anxiety. This central feature may be implicated in a large array of cognitive tasks, in particular those encompassing emotional information. Also, high trait anxiety is a common feature among anxiety disorders [Watson, 2005], and a decrease in trait anxiety is a measure of the success of psychotherapies [Fisher and Durham, 1999]. Consequently, our findings might provide potential therapeutic targets, and markers of response to treatment.

Acknowledgments

This work was supported by research grants from Bristol-Myers Squibb Company & Otsuka Pharmaceutical Company, the multi-agency thematic institute (ITMO), Pierre Houriez foundation, and the Medical Research Foundation (FRM) (FDT20140931114).

The authors declare no competing financial interests

References

Austin EJ, Deary IJ, Gibson GJ, Mcgregort MJ, Dent JB (1998): Individual response spread in self-report scales : personality correlations and consequences. Pers Individ Dif 24: 421–438 .

Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IJzendoorn MH (2007): Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol Bull 133:1–24.

Basten U, Stelzel C, Fiebach CJ (2011): Trait anxiety modulates the neural efficiency of inhibitory control. J Cogn Neurosci 23:3132–3145.

Basten U, Stelzel C, Fiebach CJ (2012): Trait anxiety and the neural efficiency of manipulation in working memory. Cogn Affect Behav Neurosci 12:571–588.

Bishop S, Duncan J, Brett M, Lawrence AD (2004a): Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat Neurosci 7:184–188.

Bishop SJ, Duncan J, Lawrence AD (2004b): State anxiety modulation of the amygdala response to unattended threat-related stimuli. J Neurosci 24:10364–10368.

Bishop SJ, Jenkins R, Lawrence AD (2006): Neural processing of fearful faces: effects of anxiety are gated by perceptual capacity limitations. Cereb cortex 17:1595–1603.

Bishop SJ (2007): Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn Sci 11:307–316.

Bush G, Luu P, Posner M (2000): Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215–222.

Campbell-Sills L, Simmons AN, Lovero KL, Rochlin AA, Paulus MP, Stein MB (2011): Functioning of neural systems supporting emotion regulation in anxiety-prone individuals. Neuroimage 54:689–696.

Comte M, Schön D, Coull JT, Reynaud E, Khalfa S, Belzeaux R, Ibrahim EC, Guedj E, Blin O, Weinberger DR, Fakra E (2014): Dissociating bottom-up and top-down mechanisms in the cortico-limbic system during emotion processing. Cereb Cortex bhu185.

Egner T, Hirsch J (2005): Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nat Neurosci 8:1784–1790.

Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J (2006): Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51:871–882.

Etkin A, Prater KE, Hoeft F, Menon V, Schatzberg AF (2010): Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. Am J Psychiatry 167:545–554.

Etkin A, Egner T, Kalisch R (2011): Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 15:85–93.

Ewbank MP, Lawrence AD, Passamonti L, Keane J, Peers PV, Calder AJ (2009): Anxiety predicts a differential neural response to attended and unattended facial signals of anger and fear. Neuroimage 44:1144–1151.

Eysenck MW, Derakshan N (2011): New perspectives in attentional control theory. Pers Individ Dif 50:955–960.

First MB, Spitzer RL, Gibbon M, Williams JBW (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP) New York: Biometrics Research, New York State Psychiatric Institute.

Fisher PL, Durham RC (1999): Recovery rates in generalized anxiety disorder following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990. Psychol Med 29:1425–1434.

Forster S, Nunez Elizalde AO, Castle E, Bishop SJ: Unraveling the Anxious Mind (2013): Anxiety, Worry, and Frontal Engagement in Sustained Attention Versus Off-Task Processing. Cereb Cortex bht248.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6:218–229.

Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, Hare TA, Bookheimer SY, Tottenham N (2013): A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. J Neurosci 33:4584–4593.

Goldstein AN, Greer SM, Saletin JM, Harvey AG, Nitschke JB, Walker MP (2013): Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. J Neurosci 33:10607–10615.

Hirsch C, Mathews A (1997): Interpretative inferences when reading about emotional events. Behav Res Ther 35:1123–1132.

Kerns JG, Cohen JD, MacDonald AW, Cho RY, Stenger VA, Carter CS (2004): Anterior cingulate conflict monitoring and adjustments in control. Science 303:1023–1026.

Kienast T, Hariri AR, Schlagenhauf F, Wrase J, Sterzer P, Buchholz HG, Smolka MN, Gründer G, Cumming P, Kumakura Y, Bartenstein P, Dolan RJ, Heinz A (2008): Dopamine in amygdala gates limbic processing of aversive stimuli in humans. Nat Neurosci 11:1381–1382.

Kim MJ, Gee DG, Loucks RA, Davis FC, Whalen PJ (2011): Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cereb Cortex 21:1667–1673.

Krug MK, Carter CS (2010): Adding fear to conflict: a general purpose cognitive control network is modulated by trait anxiety. Cogn Affect Behav Neurosci 10:357–371.

Lang PJ, Bradley MM, Cuthbert BN (2008): International affective picture System (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, FL.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233–1239.

Mathews A, Mackintosh B, Fulcher EP (1997): Cognitive biases in anxiety and attention to threat. Trends Cogn Sci 1:340–345.

Mathews A, MacLeod C (2002): Induced processing biases have causal effects on anxiety. Cogn Emot 16:331–354.

Ochsner KN, Hughes B, Robertson ER, Cooper JC, Gabrieli JDE (2009): Neural systems supporting the control of affective and cognitive conflicts. J Cogn Neurosci 21:1842–1855.

Oldfield RC (1971): The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

O'Reilly JX, Woolrich MW, Behrens TEJ, Smith SM, Johansen-Berg H (2012): Tools of the trade: psychophysiological interactions and functional connectivity. Soc Cogn Affect Neurosci 7:604–609.

Paulus MP, Feinstein JS, Simmons A, Stein MB (2004): Anterior cingulate activation in high trait anxious subjects is related to altered error processing during decision making. Biol Psychiatry 55:1179–1187.

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005): 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8:828–834.

Phillips ML, Ladouceur CD, Drevets WC (2008): A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 13:829, 833–857.

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK (2000): Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry 47:769–776.

Richards A, French CC, Calder AJ, Webb B, Fox R, Young AW (2002): Anxiety-related bias in the classification of emotionally ambiguous facial expressions. Emotion 2:273–287.

Saleem KS, Miller B, Price JL (2014): Subdivisions and connectional networks of the lateral prefrontal cortex in the macaque monkey. J Comp Neurol 522:1641–1690.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.

Shin LM, Whalen PJ, Pitman RK, Bush G, Macklin ML, Lasko NB, Orr SP, McInerney SC, Rauch SL (2001): An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biol Psychiatry 50:932–942.

Shin LM, Liberzon I (2010): The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 35:169–191.

Simmons A, Stein MB, Matthews SC, Feinstein JS, Paulus MP (2006): Affective ambiguity for a group recruits ventromedial prefrontal cortex. Neuroimage 29:655–661.

Simmons A, Matthews SC, Feinstein JS, Hitchcock C, Paulus MP, Stein MB (2008): Anxiety vulnerability is associated with altered anterior cingulate response to an affective appraisal task. Neuroreport 19:1033–1037.

Spielberger CD (1983): Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists.

Sripada RK, Marx CE, King AP, Rampton JC, Ho SS, Liberzon I (2013): Allopregnanolone elevations following pregnenolone administration are associated with enhanced activation of emotion regulation neurocircuits. Biol Psychiatry 73:1045–1053.

Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, Marcus DJ, Westerlund A, Casey BJ, Nelson C (2009): The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res 168:242–249.

Van Hoesen GW, Morecraft RJ, Vogt BA (1993): Connections of the Monkey Cingulate Cortex. In: Vogt BA and Gabriel M, editors. Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook. Boston, MA: Birkhauser. p. 249–284.

Watson D (2005): Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. J Abnorm Psychol 114:522–536.

Weinberger DR, Berman KF, Suddath R, Torrey EF (1992): Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 149:890–897.

Winterer G, Musso F, Beckmann C, Mattay V, Egan MF, Jones DW, Callicott JH, Coppola R, Weinberger DR (2006): Instability of prefrontal signal processing in schizophrenia. Am J Psychiatry 163:1960–1968.

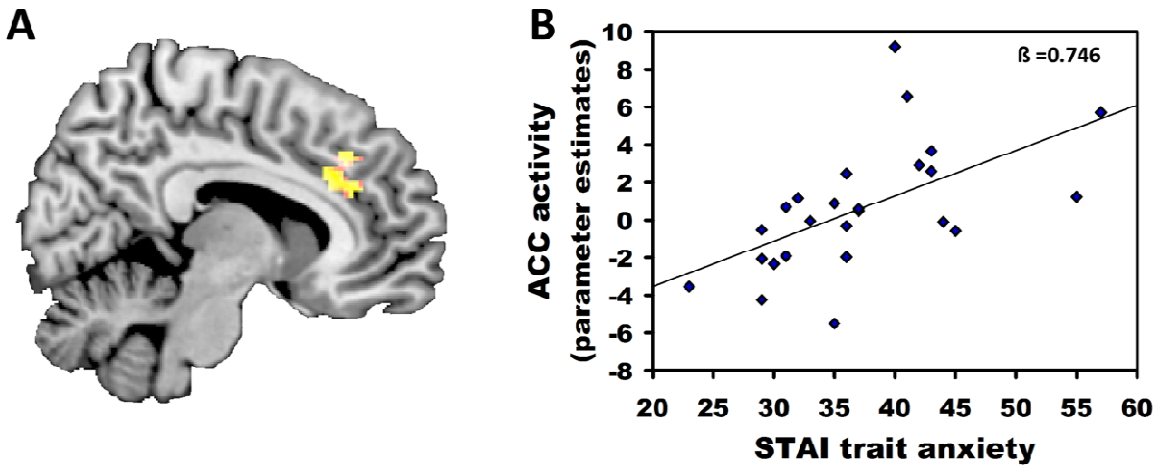

Figure 1: Effects of trait anxiety on ACC activity in incongruent compared to congruent trials. Voxels in ACC (A) showing significant positive relationship with STAI-trait scores overlaid on canonical single-subject T1 image. Activation of ACC (B) plotted against STAI-trait scores.

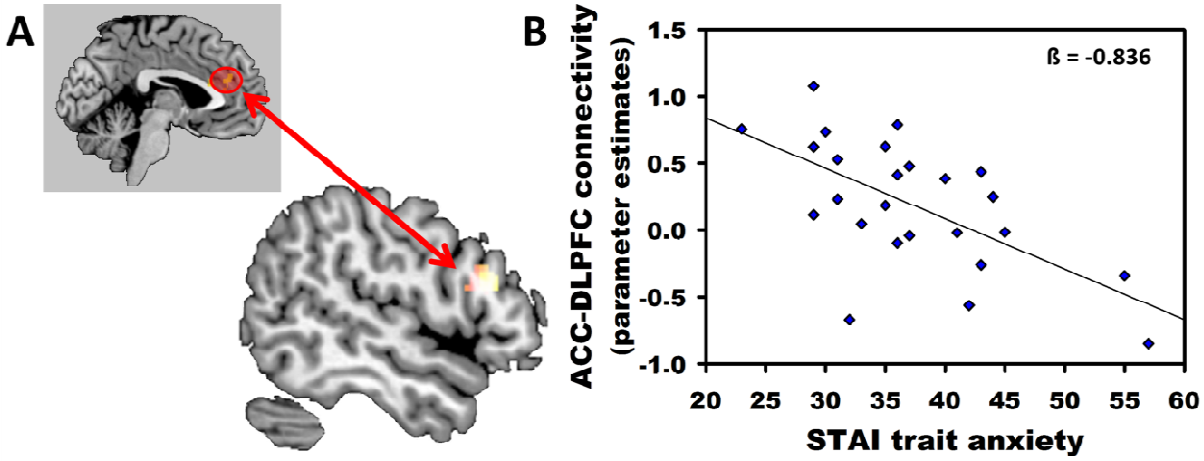

Figure 2: Effects of trait anxiety on ACC-LPFC connectivity in incongruent compared to congruent trials. A) Voxels in LPFC displaying association between STAI-trait scores and functional connectivity with ACC overlaid on canonical single-subject T1 image. B) ACC-LPFC functional connectivity plotted against STAI-trait scores.